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(71) Applicant
Sandoz Ltd

(Incorporated in Switzerland)

35 Lichtstrasse, CH-4002, Basle, Switzerland

(72) Inventors
David Bodmer
Jones Wing Fong
Thomas Kissel
Hawkins Valliant Maulding
Oskar Nagele
Jane Edna Pearson

(74) Agent and/or Address for Service
B A Yorke & Co
Coomb House, 7 St. John's Road, Isleworth,
Middlesex, TW7 6NH, United Kingdom

(54) Delayed release formulations

(57) A sustained release formulation of a peptide drug compound, preferably a somatostatin like octreotide, e.g. as a pamoate salt.

The drug compound is present in a polymeric carrier, preferably a polylactide-co-glycolide, especially a poly (lactide-co-glycolide) glucose. The formulation is preferably a depot formulation in the form of a monolithic microparticle.

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after a residence time in the polymer which protects the peptide against enzymatic and hydrolytic influences of the biological media.

Although some parenteral depot formulations of peptide drugs in a polymer in the form of microparticles or an implant, are known, satisfactory peptide release profiles are in practice only obtained in very few cases. Special measures must be taken to achieve a continuous peptide release for a therapeutically active drug serum level and if desired avoiding too high drug serum concentrations, which cause undesired pharmacological side reactions.

The peptide drug release pattern is dependant on numerous factors, e.g. the type of the peptide, and e.g. whether it is present in its free or in another form, e.g. salt form, which may influence its water solubility. Another important factor is the choice of polymer, from the extended list of possibilities which have been described in the literature.

Each polymer type has its characteristic biological degradation rate. Free carboxyl groups may be formed which contribute to the pH value in the polymer and thus additionally influence the water solubility of the peptide and thus its release pattern.

Other factors, which may influence the release pattern of the depot formulation, are the drug loading of its polymeric carrier, the manner of its distribution in the polymer, the particle size and, in case of an implant, additionally its shape. Further is the site of the formulation in the body of influence.

Until now no somatostatin composition in sustained release form for parenteral administration has reached the market, perhaps because no composition exhibiting a satisfactory serum level profile could be obtained.

with polylactide-co-glycolide polymer has been mentioned in claim 18, but no instructions have been disclosed how to obtain a continuous therapeutically active serum level.

US Patent No. 4,011,312 describes that a continuous release of an antimicrobial drug, e.g. the water soluble polymyxin B from a polylactide-co-glycolide matrix of a low molecular weight (below 2000) and a relatively high glycolide content in the form of an implant, can be obtained, when the implant is inserted into the teat canal of a cow. The drug is released within a short period of time, due to the high glycolide content and the low molecular weight of the polymer, which both stimulate a quick polymer biodegradation and thus a corresponding quick release of the drug. A relatively high drug loading content additionally contributes to a quick drug release. No somatostatins and no drug release patterns have been described.

European Patent No. 58481 discloses that a continuous release of a water soluble peptide from a polylactide polymer implant is stimulated by lowering the molecular weight of at least a part of the polymer molecules, by introducing glycolide units into the polymer molecule, by increasing the block polymer character of the polymer when polylactide-co-glycolide molecules are used, by increasing the drug loading content of the polymer matrix and by enlarging the surface of the implant.
Although somatostatins are mentioned as water soluble peptides, no somatostatin release profiles have been described and no indication has been given how to combine all these parameters to obtain e.g. a continuous somatostatin serum level over at least one week, e.g. one month.

European Patent No. 92918 describes that a continuous release of peptides, preferably of hydrophilic peptides, over an extended period of time can be obtained, when the peptide is incorporated in a conventional hydrophobic polymer matrix, e.g. of a polylactide, which is made more accessible for water by

The microparticles of this invention may be prepared by any conventional technique, e.g. an organic phase separation technique, a spray drying technique or a triple emulsion technique, wherein the polymer is precipitated together with the drug, followed by hardening of the resulting product, when the phase separation or triple emulsion technique are used.

If desired the sustained release formulations may be in the form of an implant.

We have found an especially useful modification of the phase separation technique for preparing microparticles of any drug.

Accordingly the present invention also provides a process for the production of a microparticle comprising a drug in a biodegradable, biocompatible carrier which comprises the steps of:-

a) dissolving the polymeric carrier material in an appropriate solvent, in which the drug compound is not soluble.

b) adding and dispersing a solution of the drug compound in an appropriate solvent, e.g. an alcohol, which is a non-solvent for the polymer, in the solution of step a),

c) adding a phase inducing agent to the dispersion of step b), to induce microparticle formation,

d) adding an oil-in-water emulsion to the mixture of step c) to harden the microparticle, and

e) recovering the microparticle.

We have also found an especially useful modification of the triple emulsion technique for preparing microparticles of any drug.

of the peptide drug compound therein.

c) A sustained release formulation comprising octreotide or a salt or a derivative thereof in a biodegradable, biocompatible polymeric carrier.

We have found that a novel salt of octreotide is the pamoate which is very stable in such formulations.
The present invention accordingly provides (i) octreotide pamoate and (ii) a process for the production of octreotide pamoate which comprises reacting octreotide with embonic acid (or a reactive derivative thereof).

Additionally the present invention provides:-

A method of administering a peptide to a subject which comprises administering parenterally to a subject in need of such treatment a depot formulation as defined above, especially for the treatment of acromegaly or breast cancer.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The drugs of use in the processes of the invention are preferably water soluble drugs, e.g. peptides.

The peptides of use in the processes and formulations of this invention may be a calcitonin, such as salmon calcitonin, lypressin, and the naturally occuring somatostatin and synthetic analogs thereof.

The naturally occuring somatostatin is one of the preferred compounds and is a tetradecapeptide having the structure:-

```
          *                    *
c)  (D)Phe-Cys-Tyr-(D)Trp-Lys-Val-Cys-TrpNH2
          *                    *
d)  (D)Trp-Cys-Phe-(D)Trp-Lys-Thr-Cys-ThrNH2
          *                    *
e)  (D)Phe-Cys-Phe-(D)Trp-Lys-Thr-Cys-ThrNH2
                          *                    *
f)  3-(2-(Naphthyl)-(D)Ala-Cys-Tyr-(D)Trp-Lys-Val-Cys-ThrNH2
          *                    *
g)  (D)Phe-Cys-Tyr-(D)Trp-Lys-Val-Cys-β-Nal-NH2
                        *                    *
h)  3-(2-naphthyl)-Ala-Cys-Tyr-(D)Trp-Lys-Val-Cys-β-Nal-NH2
          *                    *
i)  (D)Phe-Cys-β-Nal-(D)Trp-Lys-Val-Cys-Thr-NH2
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wherein in each of compounds a) to i) there is a bridge between the amino acids marked with a * as indicated in the next formula.

Other preferred somatostatins are:-

```
   *-----------------------------*
   |                             |
H-Cys-Phe-Phe-(D)Trp-Lys-Thr-Phe-Cys-OH
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(See Vale et al., Metabolism, 27, Supp.1, 139 (1978)).

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 *                             *
Asn-Phe-Phe-(D)Trp-Lys-Thr-Phe-Gaba
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(See European Pat.Publication No. 1295 and Appln.No. 78 100 994.9).

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   *                    *
MeAla-Tyr-(D)Trp-Lys-Val-Phe
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(See Verber et al., Life Sciences, 34, 1371-1378 (1984) and European Pat.Appln.No. 82106205.6 (published as No. 70 021)) also known as cyclo

moiety

* *

-D-Phe-Cys-Phe-DTrp-Lys-Thr-Cys- having a bridge between the Cys residues.

Particularly preferred derivatives are N^{α}-[α-glucosyl-(1-4-deoxyfructosyl]-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol and N^{α}-[β-deoxyfructosyl-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol, each having a bridge between the -Cys- moieties, preferably in acetate salt form and described in Examples 2 and 1 respectively of the above mentioned application.

The somatostatins may exist e.g. in free form, salt form or in the form of complexes thereof. Acid addition salts may be formed with e.g. organic acids, polymeric acids and inorganic acids. Acid addition salts include e.g. the hydrochloride and acetates. Complexes are e.g. formed from somatostatins on addition of inorganic substances, e.g. inorganic salts or hydroxides such as Ca- and Zn-salts and/or an addition of polymeric organic substances.

The acetate salt is a preferred salt for such formulations, especially for microparticles leading to a reduced initial drug burst. The present invention also provides the pamoate salt, which is useful, particularly for implants and the process for its preparation.
The pamoate may be obtained in conventional manner, e.g. by reacting embonic acid (pamoic acid) with octreotide e.g. in free base form. The reaction may be effected in a polar solvent, e.g. at room temperature.

The somatostatins are indicated for use in the treatment of disorders wherein long term application of the drug is envisaged, e.g. disorders with an aetiology comprising or associated with excess GH-secretion, e.g. in the treatment of acromegaly, for use in the treatment of gastrointestinal

least 2, e.g. as a mean 3 of the hydroxy groups of the polyol being in the form of ester groups, which contain poly-lactide or co-poly-lactide chains. Typically 0.2% glucose is used to initiate polymerisation. The structure of the branched polyesters is star shaped. The preferred polyester chains in the linear and star polymer compounds preferably used according to the invention are copolymers of the alpha carboxylic acid moieties, lactic acid and glycolic acid, or of the lactone dimers. The molar ratios of lactide: glycolide is from about 75:25 to 25:75, e.g. 60:40 to 40:60, with from 55:45 to 45:55, e.g. 55:45 to 50:50 the most preferred.
The star polymers may be prepared by reacting a polyol with a lactide and preferably also a glycolide at an elevated temperature in the presence of a catalyst, which makes a ring opening polymerization feasible.
We have found that an advantage of the star polymer type in the formulations of the present invention is, that its molecular weight can be relatively high, giving physical stability, e.g. a certain hardness, to implants and to microparticles, which avoids their sticking together, although relatively short polylactide chains are present, leading to a controllable biodegradation rate of the polymer ranging from several weeks to one or two months and to a corresponding sustained release of the peptide, which make a depot formulation made therefrom suitable for e.g. a one month's release.

The star polymers preferably have a main molecular weight M_w in the range of from about 10,000 to 200,000, preferably 25,000 to 100,000, especially 35,000 to 60,000 and a polydispersity e.g. of from 1.7 to 3.0, e.g. 2.0 to 2.5. The intrinsic viscosities of star polymers of M_w 35.000 and M_w 60.000 are 0.36 resp. 0.51 dl/g in chloroform. A star polymer having a M_w 52.000 has a viscosity of 0.475 dl/g in chloroform.

The terms microsphere, microcapsule and microparticle are considered to be interchangeable with respect to the invention,

polymer peptide mixture, or the mixture added to the emulsion. It is preferred that the polymer peptide mixture be added to the emulsion.

The o/w emulsion may be prepared using a emulsifier such as sorbitan mono-oleate (Span 80 ICI Corp.) and the like, to form a stable emulsion. The emulsion may be buffered with a buffer which is non-detrimental to the peptide and the polymer matrix material. The buffer may be from pH 2 to 8 with a pH 4 preferred. The buffer may be prepared from acidic buffers such as phosphate buffer, acetate buffer and the like. Water alone may be substituted for the buffer.

Heptane, hexane and the like may be used as the organic phase of the buffer.

The emulsion may contain dispersing agents such as silicone oil.

A preferred emulsion may comprise heptane, pH 4 phosphate buffer, silicone oil and sorbitan mono-oleate. When an initial drug release may be desirable, a single non-solvent hardening step may be substituted for the emulsion hardening. Heptane, hexane and the like, may be used as the solvent.

Other alternatives to the o/w emulsion may be used for hardening the microcapsules, such as:-

Solvent plus emulsifier for hardening the microcapsules without washing; and solvent plus emulsifier for hardening followed by a separate washing step.

The o/w emulsion may be used without the dispersing agent. The dispersing agent, however, avoids aggregation of the dry particles of microcapsules due to static electricity, and helps to reduce the level of residual solvent.

Examples of the solvent for the polymer matrix material include methylene chloride, chloroform, benzene, ethyl acetate, and the like. The peptide is preferably dissolved in an alcoholic

of pH 3 -8 and a solution of the polylactide-co-glycolide in methylene chloride and spraying the formed solution, emulsion or suspension of somatostatin in the polymer solution in a stream of warm air, collecting the microspheres and washing them in a buffer solution of pH 3.0 to 8.0 or destilled water and drying them in a vacuum at a temperature of from 20 to 40°C. Compared with microparticles, prepared according to the phase separation technique, they do not contain silicon oil, even not in traces, since no silicon oil is used in the spray drying technique.

The formulations of the invention may also be prepared using a triple-emulsion procedure. In a typical technique, peptide e.g. octreotide is dissolved in a suitable solvent e.g. water and emulsified intensively into a solution of the polymer, e.g. 50/50 poly(D,L-lactide-co-glycolide)glucose in a solvent, which is a non-solvent for the peptide, e.g.in methylene chloride. Examples of the solvent for the polymer matrix material include methylene chloride, chloroform, benzene, ethyl acetate, and the like.The resulting water/oil (w/o) emulsion is further emulsified into an excess of water, containing an emulsifying substance, e.g. an anionic or non-ionic surfactant or lecithin or a protective colloid e.g. gelatine, dextrin, carboxymethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, which provides continuous generation of the triple (w/o/w) emulsion. The microparticles are formed by spontaneous precipitation of the polymer and hardened by evaporation of the organic solvent. Gelatine serves to prevent agglomeration of the microspheres. After sedimentation of the microparticles the supernatent is decanted and the microparticles are washed with water and then with acetate buffer. The microparticles are then filtered and dried.

The peptide can also be dispersed directly in the polymer solution, whereafter the resulting suspension is mixed with the gelatine containing water phase.
The triple emulsion procedure is known from the US-Patent No.

formulations according to the invention, however, the so-called drug-retaining substance mentioned above, e.g. gelatine, albumin, pectin or agar, is still enclosed in the resultant microparticles.

We have now found that when the addition of the drug retaining substance (= in solution (1)) and the step of increasing the viscosity of the inner phase is avoided, and in the excess of water of the ternary $^{w}/_{o}/_{w}$-emulsion, the measure of adding an emulsifying substance or a protective colloid, like gelatine is maintained, satisfactory microparticles can still be obtained. additionally, the microparticles do not contain any drug retaining substance, and only a very small quantity of methylene chloride.

Therefore the invention provides a process for the production of microparticles prepared by intensively mixing:-

a) a solution of a drug, preferably a somatostatin, especially octreotide in an aqueous medium, preferably water or a buffer, preferably in a weight/volume ratio of 0.8 to 4.0 g / 1 to 120 ml, especially 2.5 / 10 and in a buffer of pH 3-8, especially an acetate buffer, and

b) a solution of a polymer, preferably a polylactide-co-glycolide, such as mentioned above, in an organic solvent, not miscible with the aqueous medium, e.g. methylene chloride, preferably in a weight/volume ratio of 40g/90 to 400ml, especially 40/100, preferably in such a manner that the weight/weight ratio of the drug to the polymer is from 1/10 to 50, especially 1/16 and the volume/volume ratio of the aqueous medium/organic solvent is 1/1.5 to 30, especially 1/10, intensively mixing the $^{w}/_{o}$-emulsion of a) in b) together with

c) an excess of an aqueous medium, preferably water or a buffer,

100°C and extruding and cooling the compact mass, after which the extrudate is cut and optionally washed and dried.

Conveniently the formulations according to the invention are produced under aseptic conditions.

The formulations according to the invention may be utilized in depot form, e.g. injectable microspheres or implants.

They may be administered in conventional manner, e.g. subcutaneous or intramuscular injection, e.g. for indications known for the drug contained therein.

The sustained release formulations containing octreotide may be administered for all the known indications of the octreotide or derivatives thereof, e.g. those disclosed in GB 2,199,829 A pages 89-96, as well as for acromegaly and for breast cancer.

The microparticles of this invention may have a size range from about 1 to 250 microns diameter, preferably 10 to 200, especially 10 to 130, e.g. 10 to 90 microns. Implants may be e.g. from about 1 to 10 cubic mm. The amount of drug i.e. peptide present in the formulation depends on the desired daily release dosage and thus on the biodegradation rate of the encapsulating polymer. The exact amount of peptide may be ascertained by bioavailability trials. The formulations may contain peptide in an amount from at least 0.2, preferably 0.5 to 20 per cent by weight relative to the polymeric matrix, preferably 2.0 to 10, especially 3.0 to 6% of weight.

The release time of the peptide from the microparticle may be from one or two weeks to about 2 months.

Conveniently the sustained release formulation comprises a somatostatin, e.g. octreotide in a biodegradable biocompatible polymeric carrier which, when administered to a rat

days

Triple emulsion technique:

Rat 10 mg of somatostatin/kg, subcutaneously		
retardation	(0-42 days)	> 75 %
average plasma level ($c_{p,ideal}$)	(0-42 days)	4-6.5 ng/ml
AUC	(0-42 days)	170-230 ng/ml x days

Rabbit 5 mg of somatostatin/kg, intramuscularly		
retardation	(0-42/43 days)	> 74 %
average plasma level ($c_{p,ideal}$)	(0-42/43 days)	3.5-6.5 ng/ml
AUC	(0-42/43 days)	160-270 ng/ml x days

The invention thus also provides somatostatin preferably octreotide and octreotide analog compositions, having the following properties:-

1. a retardation of at least 70%, preferably at least 74%, e.g. at least 75%, 80%, 88% or at least 89% over a period of from 0 to 42 or 43 days and/or
2. an average plasma level ($C_{p.ideal}$) of 2,5-6,5, preferably 4-6,5 ng/ml over a period of from 0 to 42 days, in the rat, when 10 mg of somatostatin is subcutaneously administered and/or an average plasma level of 3,5-6.5, e.g. 4-6,5 ng/ml over a period of from 0 to 42 or 43 days in the rabbit when 5 mg of somatostatin is intramuscularly administered and/or

3. an AUC over a period of from 0 to 42 days of at least 160, preferably of from 170-230 ng/ml x days, for the rat, when 10 mg of somatostatin is subcutaneously administered and/or an AUC over a period of from 0 to 42 or 43 days of at least 160, preferably of from 180 to 275, e.g. from 200 to 275 ng/ml x days for the rabbit, when 5 mg of somatostatin is intramuscularly administered.

poly(Dl-lactide-co-glycolide) was not exactly described.

The disclosure value of the publication is thus too low to admit it to be a prepublication, interfering with the invention.

The following examples illustrate the invention.

M_w of polymers is the mean molecular weight as determined by GLPC using polystyrene as standard.

EXAMPLE 1:

One g. of poly(D,L-lactide-co-glycolide)(50/50 molar, M_w = 45,000; polydispersity ca. 1.7) was dissolved in 15 ml of methylene chloride with magnetic stirring followed by the addition of 75 mg of Octreotide acetate dissolved in 0.5 ml of methanol. Fifteen ml of silicon oil (brand Dow 360 Medical Fluid 1000 cs) (silicone fluid) was added to the polymer-peptide mixture. The resulting mixture was added to a stirred emulsion containing 400 ml n-heptane, 100 ml pH 4 phosphate buffer, 40 ml Dow 360 Medical Fluid, 350 cs and 2 ml Span 80 (emulsifier). Stirring was continued for a minimum of 10 minutes. The resulting microparticles were recovered by vacuum filtration and dried overnight in a vacuum oven. The yield was approximately 90% of microparticles in the 10 to 40 micron size range.

The microparticles were suspended in a vehicle and administered IM in a 4 mg dose of Octreotide to white New Zealand rabbits. Blood samples were taken periodically, indicating plasma levels of 0.5 to 1.0 ng/ml for 30 days as measured by Radioimmunoassay (RIA) analysis.

EXAMPLE 2:

One g of poly(D,L-lactide-co-glycolide) glucose (M_w = 45,000 (55/45 molar produced according to the process of GB 2,145,422

for one hour, the ethanol was decanted and the microparticles were stirred with 1000 ml of n-heptane containing 1 ml of Span 80. After stirring for one hour, the microparticles were collected by vacuum filtration and dried overnight in a vacuum oven at 37 C. The residual methylene chloride level of the microparticles washed in this manner was reduced from 1.2% to 0.12%.

The combined yield of the product was 18.2 g (91%) of microparticles containing 5.6% Octreotide, mean diameter of 24 microns, 1.5% residual heptane.

The microparticles were suspended in a vehicle and injected intramuscularly in 5 mg/kg dose of Octreotide to white rabbits. Blood samples were taken periodically, indicating plasma levels of 0.3 to 7.7 ng/ml for 49 days as measured by RIA.

EXAMPLE 4:

One g of poly (D,L,-lactide-co-glycolide)glucose M_w 46,000 (50:50) molar produced according to the process of GB 2,145,422 B, Polydispersity ca. 1.7, produced from 0.2% glucose) was dissolved in 10 ml of methylene chloride with magnetic stirring followed by the addition of 75 mg of Octreotide dissolved in 0.133 ml of methanol. The mixture was intensively mixed e.g. by means of an Ultra-Turax for one minute at 20,000 rpm causing a suspension of very small crystals of Octreotide in the polymer solution.
The suspension was sprayed by means of a high speed turbine (Niro Atomizer) and the small droplets dried in a stream of warm air generating microparticles. The microparticles were collected by a "zyklon" and dryed overnight at room temperature in a vacuum oven.
The microparticles were washed with 1/15 molar acetate buffer pH4.0 during 5 minutes and dried again at room temperature in a

triple emulsion was slowly stirred for one hour. Hereby the methylene chloride was evaporated and the microcapsules were hardened from the droplets of the inner phase. After sedimentation of the microparticles the supernatant was sucked off and the microparticles were recovered by vacuum filtration and rinsed with water to eliminate gelatine.
Drying, sieving, washing and secondary drying of the microparticles was done as described for example 4.
The microparticles were suspended in a vehicle and administered i.m. in 5mg/kg dose of Octreotide to white rabbits (chinchilla-bastard) and s.c. in a 10 mg/kg dose to male rats. Blood samples were taken periodically, indicating plasma levels of 0.3 to 15.0 ng/ml (5 mg dose) in rabbits and 0.5 to 8.0 ng/ml in rats for 42 days as measured by Radioimmunoassay (RIA) analysis.

EXAMPLE 7:

Microparticles were prepared by the triple-emulsion technique in the same way as desribed for example 6 with three changes:-

1. 0.25 ml of acetate buffer pH 4.0 were used instead of 0.125 ml of water to prepare the inner W/O-phase.

2. rinsing after collection of the microparticles was carried out with 1/45 molar acetate buffer pH 4.0 instead of water.

3. further washing of microparticles was omitted.

EXAMPLE 8:

Microparticles were prepared by the triple-emulsion technique in the same way as described for example 7 with the only change that the inner W/O-phase was prepared by using water containing 0.7%(w/v) sodium chloride instead of acetate buffer.

EXAMPLE 9:

A solution of 9.9 g of poly(D,L-lactide-co-glycolide) (50/50 molar, Mw = 44,300) in 140 ml of methylene chloride was added to 100 mg of lypressin. The dispersion was magnetically stirred for one hour before adding 140 ml of silicone fluid (Dow 360 Medical Fluid, 1000 cs) and 2,5 ml of Span 80. The mixture was added to 2000 ml of heptane and stirred for 10 minutes. The resulting microcapsules were collected by vacuum filtration, washed three times with heptane, and dried 10 minutes under suction. Half of the sample was washed by stirring in water for 10 minutes; the other half was not washed. Both samples were dried overnight in a vacuum oven at 30 C. The total yield was 10.65 g of microcapsules. Analysis of the washed sample was 0.5% lypressin and 0.6% for the sample not washed with water.

retaining substance to the water-in-oil emulsion or applying any intermediate viscosity increasing step,

ii) desorbing the organic solvent therefrom,

iii) isolating and drying the resultant microparticles.

4. A process for producing microparticles comprising a drug compound in a biodegradable, biocompatible polymer, which comprises

i) intensively mixing a drug compound suspension formed from a drug compound and a water-immiscible organic solvent containing a biodegradable, biocompatible polymer with an excess of aqueous medium, containing an emulsifying substance or a protective colloid, to form an oil in water emulsion, the drug compound being dispersed in the oil component, without adding any drug retaining substance or applying any intermediate viscosity increasing step,

ii) desorbing the organic solvent therefrom,

iii) isolating and drying the resultant microparticles.

5. A process for the production of microparticles which comprises intensively mixing:-

a) a solution of a drug in an aqueous medium and

b) a solution of a polymer in an organic solvent, not miscible with the aqueous medium, intensively mixing the $^{w}/_{o}$-emulsion of a) and b) together with

c) an excess of an aqueous medium containing a protective colloid, without adding any drug retaining substance to

is from 1/10 to 50 and the volume/volume ratio of the aqueous medium/organic solvent is 1/1.5 to 30, intensively mixing the $^{w}/_{o}$-emulsion of a) in b) together with

c) an excess of water or a buffer containing a protective colloid at a volume/volume mixing speed ratio of ab) / c) of from 1/10 to 100,

without adding any drug retaining substance to the water-in-oil emulsion or applying any intermediate viscosity increasing step, hardening the embryonic microparticles in the formed $^{w}/_{o}/_{w}$-emulsion by evaporation of the organic solvent and isolating the generated microparticles.

14. A process according to claim 13, in which the protective colloid is gelatine

15. A process for the production of microparticles which comprises intensively mixing:-

a) a solution of a somatostatin in an aqueous medium in a weight/volume ratio of 2.5g/10ml and

b) a solution of a polylactide-co-glycolide in an organic solvent, not miscible with the aqueous medium in a weight/volume ratio of 40g/ 100 ml in such a manner that the weight/weight ratio of the drug to the polymer is 1/16 and the volume/volume ratio of the aqueous medium/organic solvent is 1/10, intensively mixing the $^{w}/_{o}$-emulsion of a) in b) together with

c) an excess of an aqueous medium containing a protective colloid in a concentration of 0.01 to 15.0% at a volume/volume mixing speed ratio of ab) / c) of 1/40,

biocompatible polymeric carrier.

19. A sustained release formulation of claim 18 wherein the polymer is poly-(DL-lactide-co-glycolide)glucose.

20. A formulation of claim 18 in microparticle form wherein the surface is substantially free of drug compound.

21. A sustained release formulation according to claim 18 prepared by mixing the drug compound or a solution of it in methanol or water or a buffer of pH 3 -8 and a solution of a polylactide-co-glycolide in methylene chloride and spraying the formed suspension solution or emulsion of drug compound in the polymer solution in a stream of warm air, collecting the microspheres and washing them in a buffer solution of pH 3.0 to 8.0 or distilled water and drying them in a vacuum at a temperature of from 20 to 40°C.

22. A sustained release formulation according to claim 18 in which the octreotide concentration is from 2.0 to 10% of weight.

23. A sustained release formulation according to claim 18 in microparticle form having a diameter of from 1 to 250 microns.

24. A sustained release formulation comprising a peptide drug compound in a $^{40}/_{60}$ to $^{60}/_{40}$ polyactide-co-glycolide ester of polyol, the polyol unit being chosen from the group of a (C_{3-6}) carbon chain containing alcohol having 3 to 6 hydroxyl groups and a mono- or di-saccharide, and the esterified polyol having at least 3 polylactide-co-glycolide chains.

25. A sustained release formulation comprising a peptide drug compound chosen from the group of a calcitonin, lypressin or

32. A sustained release formulation according to claim 18, 24 or 25 which when administered to a rat subcutaneously at a dosage of 10 mg of drug compound per kg of body weight exhibits an average plasma level (Cp ideal) of from 2.5 to 6.5 ng/ml over a period of from 0 to 42 days.

33. A sustained release formulation according to claim 18, 24 or 25 which when administered to a rabbit intramuscularly at a dosage of 5 mg of drug compound per kg of body weight exhibits an average plasma level (Cp ideal) of from 3.5 to 6.5 ng/ml.

34. A sustained release formulation according to claim 18, 24 or 25 which when administered to a rat subcutaneously at a dosage of 10 mg of drug compound per kg of body weight exhibits an AUC of from 160 - 230 ng/ml x days over a period of from 0 to 42 or 43 days.

35. A sustained release formulation according to claim 18, 24 or 25 which when administered to a rabbit intramuscularly at a dosage of 5 mg of drug compound per kg of body weight exhibits an AUC of from 160 to 275 ng/ml x days over a period of from 0 to 42 or 43 days.

36. A sustained release formulation according to claim 18 for use in the treatment or prevention of acromegaly or of breast cancer.

37. A method of administering a peptide drug to a subject which comprises administering parenterally to a subject in need of such treatment a depot formulation according to claim 18.

38. A method according to claim 37 for the treatment of acromegaly or breast cancer.

39. octreotide- pamoate